

# EXHIBIT E

Affidavit by Edith Mathiowitz, Ph.D.



I, Edith Mathiowitz, declare and state as follows:

**J. Relevant Expertise**

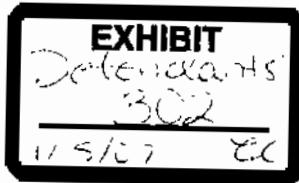
1. That I currently hold joint appointments at Brown University as Professor of Medical Science and Engineering, Department of Molecular Pharmacology & Biotechnology and as Professor of Engineering, and that I also am the Director of Graduate Program, Artificial Organs, Biomaterials and Cellular Technology.

2. That separate from my University appointments, I am currently a Consultant to and a Board Member of and previously held the positions of Chairwoman and President of Spherics, a start up company involved in drug design and drug formulation which I founded.

3. That I am well qualified to give an opinion concerning the subject matter that is claimed in the above-identified patent application which relates to controlled-release preparations of diltiazem that are designed for once-daily evening dosing (chronotherapeutic compositions).

4. That my relevant expertise is substantiated by my Curriculum Vitae which is attached as Exhibit 1 to this Affidavit. Relevant areas of my expertise which are substantiated by information contained in the Curriculum Vitae are enumerated below.

5. That for example I have substantial expertise and experience in the development of encapsulated drugs which provide for sustained, controlled release upon in vivo oral administration.



6. That I further have substantial experience in polymer chemistry and particularly the design and/or selection of biocompatible polymers appropriate for drug encapsulation which provide for desired release characteristics upon in vivo administration.

7. That I frequently am invited to speak on the subject of drug delivery systems, am the lead author on many papers on this subject, and further teach courses relating to drug delivery systems and polymers for use therein at Brown University. I am also currently one of the organizers of the Controlled Release Society.

8. That I further am an inventor on numerous patents relating to drug delivery formulations, drug containing microspheres, and polymers for use therein.

9. That based on my expertise in the art, Biovail Incorporated ("Biovail") asked that I provide my opinion concerning the subject matter claimed in patent applications 09/565,451 ("451 Application") and 09/465,338 ("338 Application") or "Biovail applications".

**K. Summary of Documents Reviewed**

10. That as part of this review I was provided and reviewed copies of the above-identified Biovail patent applications; a listing of the current claims in both of these patent applications; copies of two patent documents which were cited as prior art against these applications, i.e., EP0856313, which is assigned to Elan Corporation PLC and which names Edward James Geoghegan

et al the lead as inventor ("the '313 application or EP '313) (Exhibit 2) and WO93/00093 which is assigned to Biovail and names Arthur Deboeck et al. as the lead inventor ("the '093 Application" "WO '093") (Exhibit 3); copies of Office Actions issued by the United States Patent and Trademark Office in connection with these applications including the most recent final Office Actions wherein prior art rejections were maintained against the Biovail application claims based on the '313 Application and the '093 Application; and Biovail's responses to such Office Actions.

11. That I was further provided and reviewed technical materials identifying the exact composition of Biovail's commercial embodiments of the subject invention which comprise chronotherapeutic controlled-release preparations of diltiazem currently marketed by Biovail under the Tradename Diltiazem LA® (Exhibit 4).

12. That I further was provided and reviewed a set of proposed amended claims (Exhibit 5) which I understand are to be filed together with this Affidavit and which will replace all of the current claims contained in the subject Biovail applications. These amended claims consolidate the subject matter claimed in the Biovail '451 and '338 applications.

13. That I further was provided and reviewed a description of in vivo studies involving the administration of a diltiazem formulation corresponding to the claims being pursued in the subject Biovail patent applications (Diltiazem LA®); as well as sustained release diltiazem formulations corresponding to the patent applications cited against the subject

Biovail claims, i.e., the '093 and the '313 patent applications, wherein each of these diltiazem formulations was administered under similar conditions in the evening. (Exhibit 6 and Exhibit 7) The fact that the comparative formulations (respectively Cardiazem CD® and Tiazac®) correspond to the diltiazem formulations disclosed in the cited patent publications is evidenced by the Food and Drug Administration Orange Book listings for Cardiazem CD® and Tiazac® (Exhibit 8 and Exhibit 9) which identify United States patents 5,002,776 and 5,529,791 (which are US counterparts respectively of EP '313 and WO '093) as being US patents which cover these commercially available Diltiazem drug formulations (See Exhibit 8 and Exhibit 9). Additionally, I reviewed an exhibit containing a side-by-side comparison of the exact constituents of diltiazem formulations according to the invention (Diltiazem LA®) and diltiazem compositions according to the cited references (EP '313 and WO '093, Cardiazem CD® and Tiazac®, respectively. (Exhibit 10). Further, I reviewed another exhibit containing a side-by-side comparison of the results of in vivo studies comparing the pharmacokinetic properties of these same diltiazem formulations. (Exhibit 11) The exhibits containing these side-by-side comparisons (Exhibit 10 and Exhibit 11) were prepared at the request of Examiner Kishore at a recent interview attended by me.

14. That I further was provided and reviewed a published clinical study evaluating the clinical efficacy of a chronotherapeutic controlled release diltiazem formulation corresponding to the chronotherapeutic diltiazem formulations and methods of use being claimed by Biovail in the patent

applications at issue. This clinical study is contained in a peer-reviewed publication entitled "Efficacy and Safety of a Once Daily Graded-Release Diltiazem Formulation in Essential Hypertension", *Amer. J. Hypertension, Ltd.*, 16:51-58 (2003) (Exhibit 12).

L. Summary of Subject Matter Being Claimed in Subject Biovail Patent Applications

15. That based on the documents I reviewed, I understand that the subject matter disclosed and claimed in both of the Biovail patent applications at issue relates to orally administrable chronotherapeutic controlled-release preparations containing a pharmaceutically acceptable chronotherapeutic form of diltiazem designed for once daily administration in the evening. (See Exhibit 4).

16. That I understand that upon entry of the proposed amendment (Exhibit 5) which consolidates the subject matter being claimed in the Biovail '451 and '338 patent applications (which is to be submitted together with this Affidavit), all of the pending claims will require the following:

a controlled-release orally administrable preparation comprising at least one pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours, the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the said at least one coating covering the core comprising a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating being

comprised of (i) constituents selected from at least one lubricant and/or at least one hydrophilic polymer and (ii) further comprising as an essential constituent at least one water insoluble swellable neutral copolymer; and wherein the amount of said water swellable and diffusible coating and the specific ratios of said constituents (i) and (ii), which comprise said water swellable and diffusible coating covering said diltiazem containing core contained in said at least one bead, are formulated such that the orally administrable composition:

A) in vitro exhibits the following in vitro release characteristics;

(i) releases the diltiazem or a pharmaceutically acceptable salt thereof into a aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours;

(e) in excess of about 75% after 24 hours;

and/or (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

(a) between about 1% and about 25% after 2 hours;

(b) between about 7% and about 45% after 4 hours;

(c) between about 30% and about 68% after 8 hours;

(e) in excess of about 75% after 24 hours;

and wherein said in vitro release characteristics further result in an orally administrable composition that:

B) when given to humans exhibits the following properties:

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria;

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria; and

(iii) providing a Cmax of diltiazem in the blood at between about 10 and 15 hours after oral administration.

17. Therefore, upon entry of this amendment (Exhibit 5) all of the Biovail claims will be directed to orally administrable chronotherapeutic once-daily controlled-release diltiazem formulations and methods of use wherein said diltiazem is comprised in a core which is encapsulated in a bead coated with an amount of a water swellable and diffusible coating that is comprised of specific constituents, including in particular at least one water insoluble swellable neutral copolymer. Additionally, all the Biovail claims will further require that the amount of this water swellable diffusible coating and the specific constituents contained therein and ratios thereof are formulated such that the resultant diltiazem formulation possesses a specific combination of *in vivo* properties, *i.e.*, (i) Cmax occurs about between 10 and 15 hours after evening administration, (ii) higher bioavailability when given at night and (iii) bioequivalence when given in the morning with or without food. Still further, all of the Biovail claims will require that such compositions possess defined *in vitro* dissolution properties over the time of administration (24 hours) in two different medium aqueous and buffered medium having pH ranging from 5.5 to 6.5). It has been unexpectedly discovered by Biovail that the incorporation of an appropriate amount of a water swellable, diffusible coating, comprised of the

constituents recited in the claims, in particular including a water insoluble swellable neutral copolymer results in diltiazem formulations possessing vitro dissolution properties and further that these in vitro dissolution properties reproducibly correlate to diltiazem formulations possessing the recited in vivo properties, which render the Biovail diltiazem formulations exquisitely suited for chronotherapeutic use. In my opinion, the prior art does not suggest diltiazem compositions having the advantageous properties of the Biovial compositions which are evidenced by in vivo comparative studies of record and discussed herein.

18. That, with respect to such in vivo studies, in my opinion, Biovail's commercial embodiment (Cardiazem LA®) (See Exhibit 4), which was compared to the prior art Diltiazem formulations is representative of all the claims currently being pursued by Biovail in the '451 and '338 patent applications, as well as the subject matter that is to be claimed upon entry of the proposed amendments. (See Exhibit 5). Cardiazem LA® is representative of the claimed invention as it contains all constituents required by the Biovail claims (See Exhibit 4) and possesses the specific in vitro dissolution and in vivo pharmacokinetic properties required by the Biovail claims.

M. Comparison of Prior Art Controlled Release Diltiazem Formulations to Biovail Controlled Release Diltiazem Formulations

19. That for the reasons set forth *infra*, it is my expert opinion that neither the '313 Application nor the '093 Application teaches a chronotherapeutic controlled release diltiazem formulation containing a water

swellable and diffusible coating surrounding a diltiazem containing core comprised of specific constituents, in particular including a water insoluble swellable neutral copolymer, wherein the ratios of such constituents, and the amount of said water swellable and diffusible coating surrounding the diltiazem containing core are selected such that the resultant orally administrable composition possesses the specific combination of in vitro and in vivo properties of the chronotherapeutic controlled release diltiazem formulations and methods of use being claimed by Biovail in the subject patent applications.

20. That it is further my expert opinion that the '313 and '093 patent applications, considered alone or in combination, fail to provide any explicit or implicit teaching which would motivate or enable a skilled artisan to modify the controlled release diltiazem compositions disclosed in the '313 or '093 patent applications, in particularly to modify the coating layer described therein, *e.g.*, by variation of the polymeric constituents, ratios thereof, and/or amount of the coating layer in order to produce a controlled-release formulation of diltiazem possessing the novel combination of in vitro and in vivo properties of the orally administrable chronotherapeutic controlled-release diltiazem formulations claimed by Biovail. Particularly, I have carefully reviewed both the EP '313 and WO '093 patent disclosures and based on this review, I am of the opinion that these references alone or in combination provide no explicit or implicit incentive to produce a diltiazem formulation having the novel combination of in vitro and in vivo properties being claimed by Biovail in the patent applications at issue.

21. That more specifically, it is my expert opinion that the in vivo pharmacokinetic studies of record in the Biovail patent application which compared evening administration of a diltiazem controlled release formulation according to the Biovail invention (Diltiazem LA<sup>®</sup>) to the prior art (Cardiazem CD<sup>®</sup> (Exhibit 6), which is a commercially available controlled-release diltiazem formulation which corresponds to EP '313) and Tiazac<sup>®</sup> (Exhibit 7) (which is a commercially available chronotherapeutic controlled-release diltiazem according to WO '093) provides convincing and irrefutable evidence that the controlled-release diltiazem compositions being claimed by Biovail possess very different and clearly superior in vivo and in vitro characteristics vis-à-vis the prior art diltiazem formulations. The results of these pharmacokinetic studies are contained in Exhibit 6 and Exhibit 7 to this Affidavit and were previously submitted during prosecution of the subject Biovail applications at issue herein. Additionally, at the request of Examiner Kishore, these pharmacokinetic comparisons are further consolidated in a single exhibit, newly submitted herewith, which is attached to this Affidavit as Exhibit 11.

22. Particularly, I note that the in vivo studies (contained in Exhibit 6 and Exhibit 11), which compared evening administration of the EP' 313 formulation (Cardiazem CD<sup>®</sup>) to a formulation according to the Biovail claims (Cardiazem LA<sup>®</sup>), revealed the following significant pharmacokinetic differences between these controlled release diltiazem formulations:

(i) That the Cmax for the Biovail composition, when dosed in the evening, according to prescribed guidelines, occurred

much later (around 11 hours after evening administration) than for Cardiazem CD®, at a time when the risk of cardiac events and stroke are at their most elevated. By contrast, when dosed in the evening, Cardiazem CD® resulted in Cmax occurring 6 hours after administration.

(ii) That when the pharmacokinetic data was converted to Night/Day ratios that the pharmacokinetics of the Biovail Cardiazem LA® formulation is much better than that of Cardiazem CD® (EP '313 formulation);

(iii) That further, the Biovail Cardiazem LA® formulation provided for much higher bioavailability when dosed in the evening (*See Table 1 and 2, AUC Night/Day rate >1*) (Exhibit 6). By contrast, the Cardiazem CD® formulation exhibited lower bioavailability when dosed in the evening (*See Table 1 and 2, AUC Night/Day rate is <1* in Exhibit 6, and Exhibit 11);

(iv) That still further the Biovail Cardiazem LA® formulation provided for much lower plasma fluctuation than the Cardiazem CD® (EP '313 formulation); and

(v) That the Biovail Cardiazem LA® composition resulted in a higher Cmax when dosed in the evening than Cardiazem CD® (*See Tables 1 and 2, Exhibit 6 and Exhibit 11*).

23. That in my opinion these enumerated significant pharmacokinetic differences provide convincing evidence as to the substantial

and non-obvious differences between the subject Biovail controlled release diltiazem formulations as compared to diltiazem formulations according to EP '313 (Cardiazem CD®). I base my opinion most especially upon the fact that both of these compositions were administered in the evening under appropriate side-by-side comparison conditions. In my opinion, it is truly unexpected that the subject chronotherapeutic diltiazem composition possesses such very different pharmacokinetic properties when administered in the evening in comparison to the EP '313 formulation.

24. I further note that the in vivo studies (the results of which are contained in Exhibit 7 and Exhibit 11), which compared administration of Tiazac®, the commercial embodiment of the controlled-release diltiazem formulation disclosed in WO '093) to the Biovail chronotherapeutic diltiazem composition (Cardiezem LA®) corresponding to the claims at issue herein, again when both diltiazem formulations were administered under similar conditions in the evening, revealed the following significant pharmacokinetic differences between the subject Biovail Cardiazem LA® composition as compared to a controlled release diltiazem formulation according to WO' 093 (Tiazac®, another Biovail diltiazem formulation which is not a chronotherapeutic formulation):

(i) That when dosed in the evening the subject Biovail composition (Cardiazem LA®) resulted in Cmax diltiazem levels peaking about 11 hours after administration, i.e., diltiazem levels in the blood are the highest in the early morning hours when the risk of sudden cardiac events and stroke are similarly at their highest. By contrast, the

Tiazac® formulation (WO'093) when administered in the evening resulted in Cmax diltiazem levels occurring only about 6 hours after administration, *i.e.*, diltiazem levels in the blood peak much earlier, at a time when the risk of sudden cardiac events and strokes are not at their highest;

(ii) That a lower Cmax is achieved for Tiazac® than Cardiazem LA® when both are dosed in the evening (*See* data contained in Figure 3 and Table 3 and 4 contained in Exhibit 7 and Exhibit 11) and that the Cmax Night/Day Ratio for Tiazac® is <1 whereas for Cardiazem CD® it is >1;

(iii) That Tiazac® exhibits a higher plasma fluctuation and therefore potentially could elicit more adverse affects in patients compared to Cardiazem LA® (*See* data in Table 4 contained in Exhibit 7 and Exhibit 11); and

(iv) That Tiazac® results in a lower bioavailability when dosed in the evening compared to Cardiazem LA® (*See* Tables 3 and 4, Exhibit 7 and Exhibit 11 which show that the AUC Night/Day ratio for Tiazac® is <1 whereas for the subject chronotherapeutic formulation (Cardiazem LA® ) it is >1).

25. That in my expert opinion the above-enumerated pharmacokinetic differences between the subject Biovail chronotherapeutic controlled-release diltiazem formulation and a diltiazem formulation according

to WO' 093 provide convincing evidence as to the substantial and non-obvious differences between the subject chronotherapeutic diltiazem controlled release composition and diltiazem formulations according to WO '093. I again base my conclusions upon the fact that when both of these compositions were administered in the evening under appropriate side-by-side comparison conditions that they exhibited dramatically different pharmacokinetic properties. I believe it to be truly unexpected that the subject chronotherapeutic compositions possess such very different pharmacokinetic properties when administered under similar evening conditions. In my opinion, compositions possessing such advantageous properties are not suggested by the prior art.

26. With respect to my opinion, I further acknowledge the fact that the enhanced properties of the Biovail chronotherapeutic formulations at issue herein are apparently achieved by the nature and amount of the water swellable and diffusible coating surrounding the diltiazem drug core, which includes as an essential element at least one water insoluble, swellable neutral co-polymer, and that this water swellable, diffusible coating apparently provides for sustained pH-independent release of diltiazem from the drug containing core after administration when it is in contact with gastrointestinal fluids. I further understand based on my review of the provided relevant excerpts of the Biovail prosecution histories that the Examiner has concluded that it allegedly would have been obvious based on the cited prior art to have modified the formulations disclosed therein, in particular to modify the nature of the coating layer surrounding the diltiazem coating core, in order to obtain a water swellable,

diffusible coating containing at least one water insoluble, swellable polymer and thereby obtain a controlled-release diltiazem formulation possessing the enhanced pharmacokinetic properties of the claimed invention. I respectfully but vigorously disagree.

27. That I vigorously disagree because in my opinion neither EP '313 nor WO '093 provides any teaching or suggestion regarding the problem addressed and solved by Biovail, namely the production of a truly chronotherapeutic diltiazem formulation, *i.e.*, one which when administered in the evening every 24 hours results in enhanced pharmacokinetic properties, most especially Cmax diltiazem levels being attained in the early morning hours when the risk of sudden cardiac events and stroke are at their most elevated. Both of the cited publications are completely silent with respect to a chronotherapeutic composition possessing such properties or the need and intrinsic advantages of a diltiazem formulation possessing such properties.

28. That even assuming that the cited publications were not silent with respect to the problems solved by the present invention, contrary to the position taken by the Patent Office, it is my opinion, based on my substantial relevant experience in drug formulation and expertise in polymer chemistry and the use thereof in drug coatings, it could not have been reasonably anticipated that the incorporation of a sufficient amount of a coating layer comprising at least one water insoluble swellable neutral co-polymer (*e.g.*, a water-, acid, base-insoluble polymer of a neutral acrylic polymer; a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate; or a neutral copolymer without any

functional groups that form water insoluble films) would have resulted in a chronotherapeutic diltiazem formulation possessing the novel and superior pharmacokinetic properties of the subject chronotherapeutic diltiazem formulations.

29. That my opinion is supported by my substantial experience in drug formulation and drug encapsulation techniques, as well as the design and selection of polymers for use in sustained release drug formulations having desired in vivo pharmacokinetic properties and in vitro release properties. That my experience has instead shown that the formulation of orally administrable sustained release drug formulations possessing a requisite combination of in vitro dissolution properties and in vivo pharmacokinetic properties is highly complex and unpredictable. For example, whereas one drug encapsulation system may achieve desired pharmacokinetic properties for a particular drug, it may be totally unsuitable for another drug, or may need to be substantially modified. Also, I can well attest to the fact that in vitro dissolution properties for a particular drug formulation do not necessarily or predictably correlate to desired in vivo pharmacokinetic properties. By contrast, the design of a drug delivery system which achieves a desired combination of in vitro dissolution characteristics which correlate to desired in vivo pharmacokinetic properties typically requires much trial and error experimentation, e.g., variation of polymeric and/or other constituents that constitute the coating layer or layers, variation of the amounts thereof, variation of the active particle size, variation of the amount of encapsulated active, variation of formulation methods, and the

like, and systematically evaluating whether any of such variations result in an orally administrable drug formulation possessing desired in vitro dissolution properties and in vivo properties.

30. That based on the unpredictability and complexity generally associated with the design of sustained drug delivery formulations having a desired set of in vitro and in vivo properties, it is my opinion that while it might have been "obvious to try" to vary the polymers and other constituents in the coating material, the ratios thereof, and/or the amount of the coating layer, that the effects of such modifications on in vitro release characteristics and in vivo pharmacokinetic properties of the resultant diltiazem formulation were far from obvious.

31. That it further is my expert opinion that EP '313 provides no motivation to substitute a neutral copolymer for any of the charged copolymers contained in the EP '313 diltiazem formulation. With respect thereto, the Table (Exhibit 13), submitted during prosecution of the Biovail applications at issue reveals that every Eudragit co-polymer mentioned in EP '313 is a charged co-polymer. Moreover, as shown in the attached pages from the Handbook of Pharmaceutical Excipients, Fourth Edition, Edited by Raymond C. Rowe et al., 2003 (Exhibit 14), it can be seen that all of the specific Eudragit copolymers exemplified in EP '313 are charged in the pH range inherent to the gastrointestinal tract. (*See especially* pages 463-465 of Exhibit 14). Moreover, based on my review of the reference, EP '313 provides no suggestion to substitute the exemplified charged Eudragit copolymer with an uncharged copolymer which

provides for pH-independent drug release as contained in the Biovail diltiazem formulations. Moreover, I disagree with the Patent Officials' position that EP'313 would generically suggest all types of Eudragit copolymers, including neutral co-polymers. To the contrary, one skilled in the relevant art such as myself, reading the EP'313 disclosure, would instead conclude that their invention requires the use of a charged Eudragit copolymer. My conclusion is supported by the fact that neutral and charged copolymers are not equivalent and do not provide equivalent results. By contrast, the water insoluble, swellable neutral co-polymer which is contained in the coating layer that surrounds the drug containing core in the subject diltiazem formulations, because of its neutral uncharged nature, results in a diffusible coating layer that facilitates prolonged pH-independent release of the drug from the drug containing core when it is in contact with gastrointestinal fluids. This pH-independent drug release in turn facilitates the desired result, *i.e.*, C<sub>max</sub> levels of diltiazem being attained after evening administration in the morning hours when cardiac events are most likely to occur. However, while this outcome was hoped for, it was hardly reasonably anticipated given the highly complex and numerous unpredictable factors that are associated with the design of sustained release drug delivery compositions possessing a desired set of *in vitro* and *in vivo* properties. In my opinion, it is not suggested by EP '313, nor could it have been reasonably anticipated that the incorporation of a neutral co-polymer in the coating layers in lieu of a charged co-polymer would have resulted in chronotherapeutic diltiazem formulations possessing the novel combination of in

vitro and in vivo characteristics possessed by the Biovail claimed invention, which differ dramatically from diltiazem formulations according to EP'313.

32. I also understand that the Examiner at the recent interview criticized the fact that only one water insoluble, swellable neutral co-polymer was exemplified in the subject application. The Examiner seemed to question whether a skilled artisan would be able to select other appropriate water insoluble, swellable neutral co-polymers suitable for use in the Biovail invention. With respect thereto, it is my expert opinion that a skilled artisan, based on the teachings of the subject application, would be able to select other suitable water swellable neutral co-polymers and obtain diltiazem formulations having the desired combinations of in vitro and in vivo pharmacokinetic properties. For example, I am aware of Kollicoat® SR 30D, another water insoluble swellable neutral co-polymer, commercially available from BASF, that is biocompatible and which is suitable for use in coatings and sustained-release coated drug formulations. (See Exhibits 15 and 16).

33. I also understand with respect to the showing of unexpected results contained in Exhibit 6 and Exhibit 11 that the Examiner has suggested that the comparative results are not commensurate in scope with the claims and further do not constitute an appropriate comparison because the dosage of diltiazem in the Biovail Cardiazem LA® composition is not the same as the comparison composition (Cardiazem CD®). I respectfully disagree.

34. I have reviewed all of the Biovail claims and compared these claims to the description of the commercial Biovail formulation used in the

comparison (Cardiazem LA®). (See Exhibit 4 and Exhibit 5). In my opinion, the exemplified Cardiazem LA® formulation corresponds to and is representative of all of the claims being pursued by Biovail.

35. That I further understand from my review of the prosecution history that the Examiner has concluded that the in vitro release characteristics of the claimed chronotherapeutic compositions (as recited in the Proposed Amended Claims) corresponds to that possessed by the prior art. I vigorously disagree. In my opinion, the dissolution ranges recited in the claims at issue herein clearly show that the claimed chronotherapeutic compositions possess very different dissolution properties in two different media, i.e., an aqueous medium and a buffered medium having a pH which ranges from pH 5.5 to 6.5. These differences are illustrated by the dissolution data of record comparing the dissolution profile of a Diltiazem formulation according to the claims (Cardiazem LA) to a Diltiazem formulation according to the prior art (Cardiazem CD and Tiazac). This data was obtained in two different media using the same in vitro dissolution testing procedures specified in the claims at issue. In my opinion this data establishes unequivocably that there exists clear and significant differences between the in vitro dissolution profiles of the subject chronotherapeutic diltiazem formulations versus the prior art diltiazem formulations. Furthermore this data supports Applicants' arguments made during prosecution that it is improper to compare dissolution profiles conducted in different dissolution media having different pH ranges as they often differ dramatically. Indeed this is why when orally administrable sustained release formulations are produced that

their dissolution properties must be tested in different dissolution media so as to take into account the disparate pH conditions inherent to the GI tract.

36. That I further believe that the provided comparison establishes that the advantages achieved by the Biovail composition are not a function of increased dosage or potency. In fact, in the provided comparison (Exhibit 6) Biovail clearly states that in order to "normalize for the difference in dosage strength of the two diltiazem formulations" the data was presented "as Night/Day ratios" This is similarly clear from Exhibit 11. Therefore, it is apparent based on the in vivo pharmacokinetic comparative studies already of record and newly submitted in Exhibit 11 that the enhanced pharmacokinetic properties of the Biovail formulation (as exemplified by Cardiazem LA®) relative to the EP '313 composition (Cardiazem CD®) are not attributable to the administration of a higher diltiazem dose as suggested by Patent Examiner. Rather, as discussed above, the enhanced results are believed to be attributable to the combination of constituents contained in the coating layer comprised in the claimed sustained release diltiazem formulations, in particular the swellable neutral copolymer, as well as the formulation and amount of such coating layer relative to other constituents in the subject diltiazem formulations.

N. The Prior Art Rejections Should Be Withdrawn Because the Subject Invention Achieves Results Which Correlate to Enhanced Clinical Efficacy

37. For the reasons enumerated above, it is my expert opinion that neither EP '313 nor WO '093 teaches or provides the requisite motivation to produce a truly chronotherapeutic diltiazem controlled release composition,

which when administered in the evening, every 24 hours, exhibits the combination of in vitro and in vivo properties recited in the Biovail claims. In my opinion, the enhanced properties of the Biovail compositions vis-à-vis the prior art are highly significant since these differences result in a diltiazem medicament which exhibits greater clinical efficacy, i.e., a medicament which should elicit reduced side effects (because of lower blood plasma fluctuation) and which medicament should better prevent sudden heart events and stroke in patients when the risks are at their most elevated. As noted previously, in my opinion, it has been abundantly demonstrated that the administration of a Biovail diltiazem formulation as claimed herein results in Cmax diltiazem levels peaking in the early morning (when administered in the evening, as directed), i.e., about 10-15 hours after administration. The enhanced clinical efficacy of the subject Biovail diltiazem formulations (which I believe to be attributable to the nature and amount of the coating layer) is further apparent from the clinical study contained in Exhibit 12 which compared the efficacy and safety of a chronotherapeutic diltiazem formulation according to the Biovail claims (Diltiazem LA<sup>®</sup>) at different dosages (120, 240, 360 and 540 mg amounts) administered at bedtime in a 7-week randomized, double-bind comparison to a placebo, and the same formulations administered once-daily in the morning (8 AM).

38. The results of this clinical study revealed that subjects administered the inventive chronotherapeutic diltiazem according to the invention in the evening exhibited dose-related mean reductions in mean

diastolic blood pressure between 6 AM and 12 noon compared to morning administration, as well as exhibiting similar reductions in systolic blood pressure. Based on these results, the authors of this study concluded that administration of Biovail's chronotherapeutic compositions as directed in the evening obtained greater reduction of blood pressure in the early morning hours (between 6 AM and 12 noon) when circadian blood pressure is at its highest, and furthermore provides a safe, well tolerated therapeutic option for patients with severe hypertension. Given the well known correlation of hypertension to the onset of sudden cardiac events and stroke, this study provides compelling evidence that the present invention provides controlled release diltiazem formulations having enhanced clinical efficacy, which should correlate to a reduction of heart attacks and stroke in patients using the Biovail claimed compositions according to the prescribed guidelines (evening administration). This is a very significant result which can not be down played because such adverse events can often be fatal or life threatening. Therefore, for the reasons set forth herein, it is my opinion that the chronotherapeutic controlled release diltiazem formulations which are claimed in the subject Biovail patent applications provide a significant advance in the art which has resulted in improved therapies for the prevention of heart attack and other adverse cardiac events.

O. The Prior Art Rejections Should Further Be Withdrawn Based on Additional Secondary Considerations (Commercial Success)

39. I further note that the unexpected results and advantages of the subject Biovail orally administrable chronotherapeutic diltiazem

formulations are evidenced by commercial success. In particular I understand that the annual sales for Cardiazem LA® in 2003 were \$47.7 million whereas in 2004 they went up to \$54.3 million dollars, *i.e.*, a 14% increase in sales from the prior year (which correlates to about 1,350,000 prescriptions annually). In my opinion the high sales and increasing number of prescriptions of Diltiazem LA® can be attributed to the enhanced pharmacokinetic and clinical properties of this diltiazem formulation vis-à-vis other commercially available diltiazem formulations for the reasons discussed supra.

40. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Date: 4/10/05

By: Edith Mathiowitz  
Edith Mathiowitz, Ph.D.

360619

# EXHIBIT F

# EXHIBIT 6

In Vivo Comparison  
of  
Cardiazem LA®  
and  
Cardiazem CD®

not have deviated from the teachings of EPA '313 to use a neutral copolymer as there is no motivation provided by the teachings of EPA '313 to use a neutral copolymer.

The Examiner has recommended a side-by-side comparison of the EPA '313 formulation to that of Applicant's claimed formulation. Applicant has now compared pharmacokinetic parameters of the preparation as claimed in the instant application (currently marketed as Cardizem LA), which is limited to a neutral copolymer, to the product described in EPA '313 (see Tables 1 and 2 and Figures 1 and 2). EPA '313 is equivalent to US 5,002,776, which is listed in the FDA Orange Book for Cardizem CD. The pharmacokinetic data for Cardizem CD has been published in Thiffault et al. (previously submitted to the Examiner - should the Examiner require a copy of this reference, please advise):

Parameters	<u>Table 1</u>			
	<u>Cardizem LA 360 mg</u>		<u>Cardizem CD 240 mg*</u>	
	<u>Day</u>	<u>Night</u>	<u>Day</u>	<u>Night</u>
AUC <sub>0-t</sub>	<u>3691 ± 1449</u>	<u>4251 ± 1219</u>	<u>2008 ± 814</u>	<u>1754 ± 715</u>
C <sub>max</sub>	<u>274.5 ± 149.0</u>	<u>290.9 ± 94.0</u>	<u>137.7 ± 48.6</u>	<u>127.6 ± 47.8</u>
Plasma Fluctuation	<u>118.9 ± 70.8</u>	<u>93.6 ± 29.5</u>	<u>112.5 ± 25.5</u>	<u>125.8 ± 31.2</u>

a - data based on Thiffault article

AUC<sub>0-t</sub> = Steady-state area under the curve, t = dosing interval = 24 hours

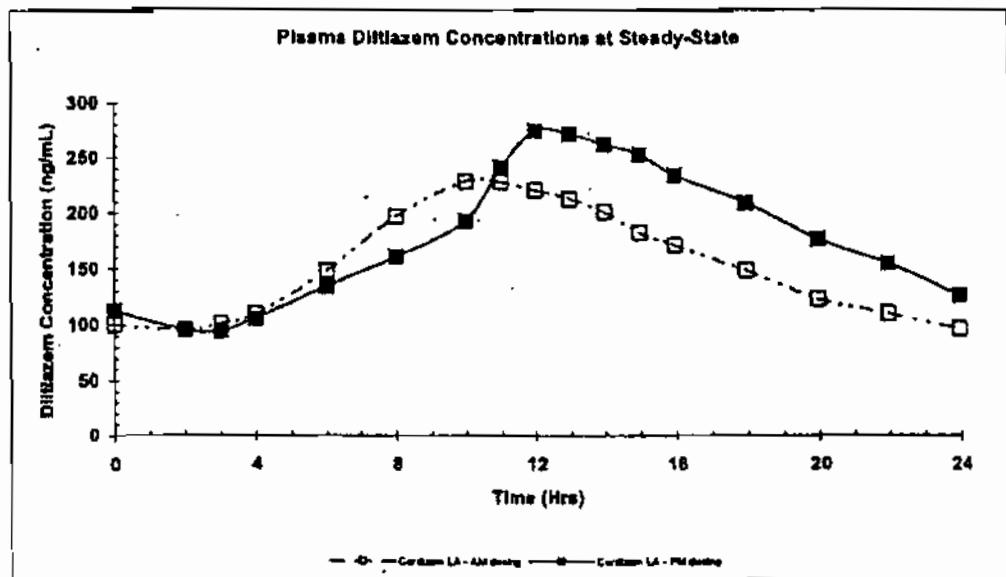
To normalize for the differences in dosage strength of the two diltiazem preparations, the above data is presented below in Table 2 as a Night/Day ratio:

Table 2

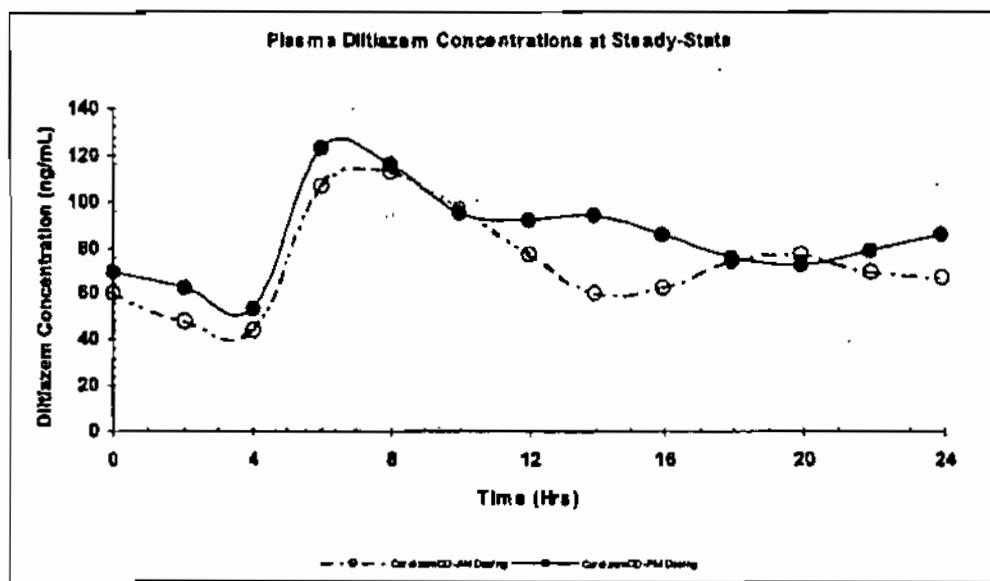
Parameters	Night/Day Ratio	
	<u>Cardizem LA</u>	<u>Cardizem CD</u>
AUC	1.15	0.874
C <sub>max</sub>	1.06	0.927
Plasma Fluctuation	0.787	1.12

Table 1 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 1 is converted to Night/Day ratios of the pharmacokinetic parameters it is quite clear that the pharmacokinetics of LA is better than that of CD (Table 2). The LA formulation provides for a much higher bioavailability (both AUC and  $C_{max}$  are  $>$  than 1) and lower plasma fluctuation ( $< 1$ ) during the night than CD.

**Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg**



**Figure 2: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem CD 240 mg**



#### LA-PM vs. AM DOSING

Figure 1 together with Tables 1 and 2 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begins to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher  $C_{max}$  is reached when dosed in the evening (see also Tables 1 and 2),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 1 and 2, AUC Night/Day ratio >1}. The higher

bioavailability of diltiazem from the LA formulation translates to higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to CD (see Table 2).

#### CD PM vs. AM DOSING

Figure 2 together with Tables 1 and 2 show that:

1. CD when dosed at night begins to increase around 4 hrs after administration and peaks about 6 hrs after administration. Thus, dosing CD around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower  $C_{max}$  is reached when dosed in the evening compared to LA (almost half of LA, see Figure 2 and Tables 1 and 2,  $C_{max}$  Night/Day ratio is < 1),
3. A lower bioavailability is achieved when dosing in the evening compared to LA (see Tables 1 and 2, AUC Night/Day ratio is < 1), CD exhibits much higher plasma fluctuation and hence more adverse effects compared to LA (see Table 2).

The above data clearly show the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer, compared to the product described by EPA '313, which teaches the use of charged copolymers of acrylic and methacrylic acid ester polymers and neither teaches nor suggests the use of a neutral copolymer. Further, EPA '313 neither teaches nor suggests the night-time effect of administering its product on the bioavailability of diltiazem. This effect would not be inherent to the EPA '313 product as the pharmacokinetics of the product disclosed in EPA '313 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected

# EXHIBIT G

# EXHIBIT 7

In Vivo Comparison  
of  
Cadiazem LA®  
and  
Tiazac®

Applicant respectfully submits, one needs to recognize the problem, see, for example, *Monarch Knitting Machine Corporation v. Solzer Morat GmbH*, 45 USPQ 2d (1977), 1981-1982 (Fed. Cir. 1998)

"where the District Court's formulation of the problem confronting the '053 inventors presumes the solution to the problem - modification of the stem segment. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. See, EG *In re Antal*, 58 CCPA 1382 444 F.2d 1168, 1171-72, 170 USPQ, 285, 287-88 (CCPA 1971)."

Therefore, again, Applicant respectfully submits WO '093 does not render obvious Applicant's invention. This is clearly shown in the data below where pharmacokinetic parameters of the preparation as claimed in the instant application currently marketed as Cardizem LA, which is limited to a neutral copolymer to the product described in WO '093 (see Tables 3 and 4 and Figures 1 and 3). WO '093 is equivalent to US 5,529,791, which is listed in the FDA Orange Book for Tiazac. Tiazac is not a chronotherapeutic product as clearly spelled out in Figure 8 of Applicant's application.

Parameters	Table 3			
	<u>Cardizem LA 360 mg</u>		<u>Tiazac 360 mg<sup>b</sup></u>	
	<u>Day</u>	<u>Night</u>	<u>Day</u>	<u>Night</u>
AUC <sub>0-<math>\tau</math></sub>	3691 ± 1449	4251 ± 1219	2870 ± 1005	2754 ± 810
C <sub>max</sub>	274.5 ± 149.0	290.9 ± 94.0	243.2 ± 79.0	200.3 ± 59.1
Plasma Fluctuation	118.9 ± 70.8	93.6 ± 29.5	171.4 ± 43.8	144.8 ± 26.7

b - Data based on Bioclin Research Laboratories Analytical Report. Report is available should the Examiner request it.

AUC<sub>0- $\tau$</sub>  = Steady-state area under the curve,  $\tau$  = dosing interval = 24 hours

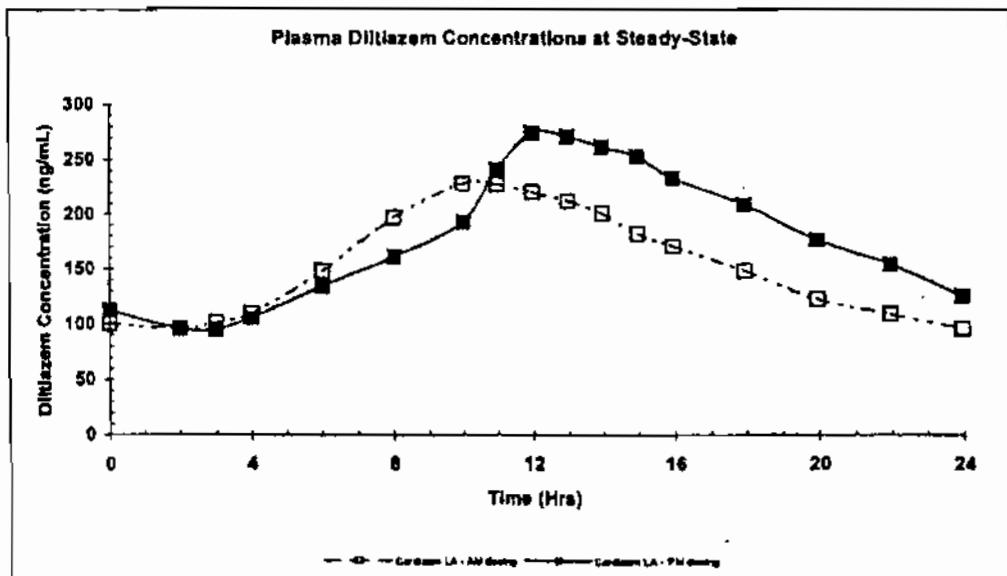
Table 4 below provides night/day ratio

Parameters	Table 4	
	Night/Day Ratio	
	Cardizem LA	Tiazac
AUC	1.15	0.960
C <sub>max</sub>	1.06	0.824
Plasma Fluctuation	0.787	0.845

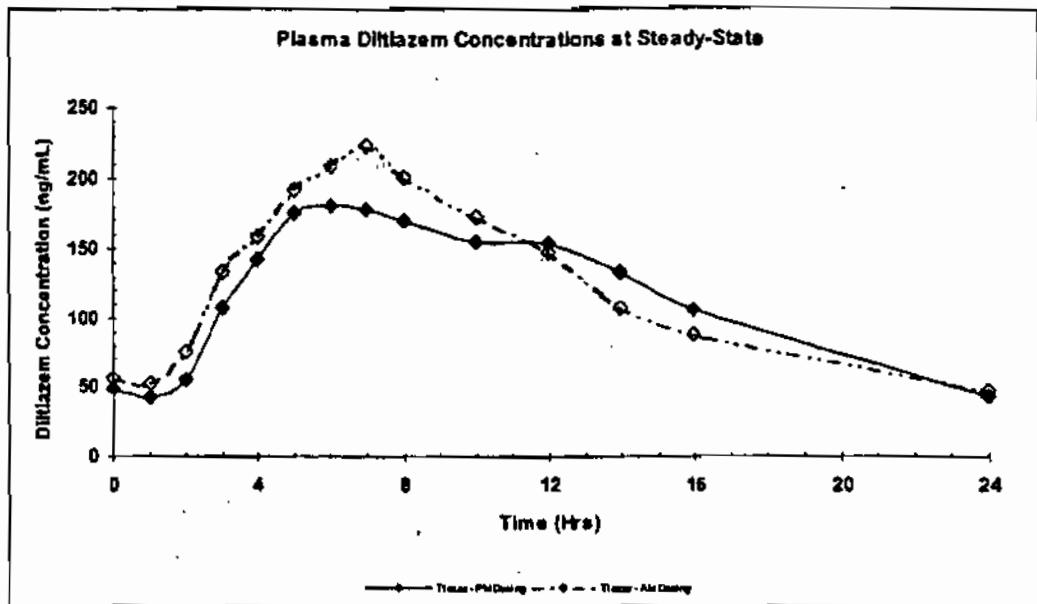
Table 3 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 3 is converted to night/day ratios of the pharmacokinetic parameters, it is quite clear that the pharmacokinetics of LA is better than that of Tiazac (Table 4). The LA formulation provides for a much higher bioavailability, both area under the curve and C<sub>max</sub> are greater than 1 and lower plasma fluctuation during the night than Tiazac.

For ease of reference and comparison, Figure 1 is re-produced below:

Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg



**Figure 3: Mean Steady-State Diltiazem Concentrations Following Administration of Tiazac 360 mg**



#### LA-PM vs. AM DOSING

Figure 1 together with Tables 3 and 4 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begin to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher  $C_{max}$  is reached when dosed in the evening (see also Tables 3 and 4),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 3 and 4, AUC Night/Day ratio >1). The higher

[REDACTED]  
bioavailability of diltiazem from the LA formulation translates to  
higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to Tiazac (see Table 4).

#### **TIAZAC PM vs. AM DOSING**

Figure 3 together with Tables 3 and 4 show that:

1. Tiazac when dosed at night begins to increase around 2 hrs after administration and peaks at about 6 hrs after administration. Thus, dosing Tiazac around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower Cmax is reached when dosed in the evening compared to LA (see Figure 3 and Tables 3 and 4, Cmax Night/Day ratio is <1),
3. A lower bioavailability is achieved when dosed in the evening compared to LA (see Tables 3 and 4, AUC Night/Day ratio is <1),
4. Tiazac exhibits a higher plasma fluctuation and hence more adverse effects compared to LA (see Table 4).

The above data clearly shows the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer compared to the product described by WO '093. WO '093 does not teach or suggest a night time effect of administering its product on the bioavailability of diltiazem. Further, this effect would not be inherent to the WO '093 product as the pharmacokinetics of the product disclosed in WO '093 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected novel features of the instantly claimed invention result in the true chronotherapeutic formulation. Therefore, Applicant's invention clearly exhibits unexpected results. Furthermore, the above comparison, Applicant respectfully submits, addresses the Examiner's concern that the previous data submitted regarding Tiazac was

concerning a 240 mg formulation and the data regarding Applicant's claimed formulation was based on a 300 mg capsule. Now, the comparison to Tiazac, as well as to the Applicant's formulation, are now based on the same dosage amount, thus satisfying the Examiner's request.

Given the facts provided above, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case for obviousness in view of EPA '313 and in view of WO '093. Again, the Applicant refers the Examiner to the data presented above showing the unexpected results obtained when a neutral copolymer is used.

Applicant respectfully reminds the Examiner that the criteria for obviousness determinations are well established in US Patent Law and have been set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). To establish obviousness based on a combination of the elements disclosed in the prior art there must be some motivation suggested in their teaching of the desirability of making the specific combination that was made by the Applicant. See In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000), citing In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) and In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

While the Examiner asserts that "One of ordinary skill in the art would have been motivated to manipulate the formulation based on the specifics of the desired formulation", the Examiner has not provided any analysis regarding how any one of the references should be modified to arrive at the claimed invention. Rather, the Examiner provides the conclusory statement that it would have been obvious to one of ordinary skill in the art at the time of the invention to create a controlled release formulation of diltiazem based on the teachings of EPA '313 or WO '093 with the reasonable expectation of producing a composition that would exhibit Applicants'

# EXHIBIT H

**THIS EXHIBIT HAS BEEN  
REDACTED IN ITS ENTIRETY**